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Bezeichnung:	Pharmaceutical combination for the prevention or treatment of cardiovascular, cardiopulmonary, pulmonary of renal diseases
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Die angehefteten Stücke sind eine richtige und genaue Wiedergabe der ursprünglichen Unterlagen dieser Patentanmeldung.

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Deutsches Patent- und Markenamt
Der Präsident
Im Auftrag

Kahle

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PHARMACEUTICAL COMBINATION FOR THE PREVENTION OR TREATMENT OF CARDIOVASCULAR, CARDIOPULMONARY, PULMONARY OR RENAL DISEASES

Field of the Invention

This invention relates to: a method for the prevention or treatment of cardiovascular, cardiopulmonary, pulmonary or renal diseases, which method comprises co-administration of effective amounts of telmisartan and atorvastatin, or of polymorphs or salts thereof, to a person in need of such treatment; suitable pharmaceutical compositions comprising telmisartan and atorvastatin, or polymorphs or salts thereof, as a combined preparation for simultaneous, separate or sequential use in the prevention or treatment of said diseases; the combined use of telmisartan and atorvastatin, or polymorphs or salts thereof, for the manufacture of a pharmaceutical composition for the prevention or treatment of said diseases.

Background of the Invention

Angiotensin II (ANG II) plays a major role in pathophysiology, especially as the most potent blood pressure increasing agent in humans. It is known that ANG II, besides its blood pressure increasing effect, additionally features

growth promoting effects contributing to left ventricular hypertrophy, vascular thickening, atherosclerosis, renal failure and stroke. Bradykinin, on the other hand, exerts vasodilating and tissue protective actions.

ANG II antagonists, therefore, are suitable for treating elevated blood pressure and congestive heart failure in a mammal. Examples of ANG II antagonists are described in EP-A-0 502 314, EP-A-0 253 310 , EP-A-0 323 841, EP-A-0 324 377, US-A-4,355,040 and US-A-4,880,804. Examples of ANG II antagonists are candesartan, eprosartan, irbesartan, losartan, olmesartan, tasosartan, valsartan, or telmisartan.

The antihypertensive and renoprotective effects of ANG II antagonists are, for example, disclosed in the following publications:

W. Wienen et al.: Antihypertensive and renoprotective effects of telmisartan after long term treatment in hypertensive diabetic (D) rats, 2nd. Int. Symposium on Angiotensin II Antagonism, February 15-18, 1999, The Queen Elizabeth II Conference Center, London, UK, Book of Abstracts, Abstract No. 50;

J. Wagner et al.: Effects of AT_1 receptor blockade on blood pressure and the renin angiotensin system in spontaneously hypertensive rats of the stroke prone strain, Clin. Exp. Hypertens. 1998, 20: 205-221; and

M. Böhm et al.: Angiotensin II receptor blockade in TGR(mREN2)27: effects of renin-angiotensin-system gene ex-

pression and cardiovascular functions, J. Hypertens. 1995, 13 8: 891-899.

Further renoprotective effects of ANG II antagonists found within first clinical trials are, for example, disclosed in the following publications:

S. Andersen et al.: Renoprotective effects of angiotensin II receptor blockade in type 1 diabetic patients with diabetic nephropathy, Kidney Int. 57 (2), 601-606 (2000);

L.M. Ruilope: Renoprotection and renin-angiotensin system blockade in diabetes mellitus, Am. J. Hypertens. 10(12 PT 2) Suppl.), 325S-331S (1997);

J.F.E. Mann: Valsartan and the kidney: Present and future, J. Cardiovasc. Pharmacol. 33 Suppl. 1, S37-S40 (1999);

Furthermore, effects of ANG II antagonists on endothelial dysfunction are, for example, disclosed in the following publications:

E.L. Schiffrin et al.: Correction of arterial structure and endothelial dysfunction in human essential hypertension by the angiotensin receptor antagonist losartan, Circulation 101(14), 1653-1659 (2000);

R.M. Touyz et al.: Angiotensin II stimulates DNA and protein synthesis in vascular smooth muscle cells from human arteries: role of extracellular signal-regulated kinases, J. Hypertens. 17(7), 907-916 (1999);

E.L. Schiffrin: Vascular remodelling and endothelial function in hypertensive patients: Effects of antihypertensive therapy, Scand. Cardiovasc. J. 32 Suppl. 47, 15-21 (1998); and

A. Prasad: Acute and chronic angiotensin-1 receptor antagonism reverses endothelial dysfunction in atherosclerosis, Circulation 2000, 101: 2349 cont.

It is also known that ANG II antagonists selectively block the AT_1 receptor, leaving the AT_2 receptor, which plays a role in anti-growth and tissue regenerative actions, unopposed.

EP-A-1 013 273 further discloses the use of AT_1 receptor antagonists or AT_2 receptor modulators for treating diseases associated with an increase of the AT_1 receptors in the sub-epithelial area or an increase of the AT_2 receptors in the epithelia, especially for the treatment of several lung diseases.

In other respects, it has been observed that hypertension frequently coexists with hyperlipidemia, and both are considered to be major risk factors for developing cardiovascular diseases, which result often in adverse cardiovascular events.

High levels of blood cholesterol and blood lipids are involved in, for example, the onset of atherosclerosis, a condition characterised by irregularly distributed lipid deposits in the intima of arteries, including coronary, carotid and peripheral arteries.

This irregular lipid distribution is also characteristic of coronary heart disease, a cardiovascular disease in which the severity and incidence has been shown to be also affected by the presence of diabetes, the sex of the subject, cigarette smoking and left ventricular hypertrophy secondary to hypertension (Wilson et al., Am. J. Cardiol., 1987, Vol. 59(14), pp. 91G-94G).

Angina pectoris, a condition characterised by a severe constricting pain in the chest, frequently radiating from the precordium to the left shoulder and down the left arm, often also requires a combined therapy with a lipid lowering agent, together with beta-blockers, nitrates or calcium channel blockers. Often, angina pectoris is due to ischemia of the heart and is usually caused by coronary disease. If treated wit surgical procedures, angina pectoris patients frequently experience complications such as restenosis, manifested either as a short term proliferative response to angioplasty-induced trauma or as long term progression of the atherosclerotic process in both graft vessels and angioplastied segments.

Some therapies for lowering lipids and cholesterol are based on an inhibition of the activity of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), an enzyme which catalyses the conversion of 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, an early step in the cholesterol biosynthetic pathway.

Known inhibitors of the HMG-CoA reductase are, for example, the compounds derived from a fungal metabolite and

with approved names ending with "statin", such as pravastatin, lovastatin, fluvastatin, simvastatin or atorvastatin.

Atorvastatin, for example, is known as a potent inhibitor of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) and as a highly liver-selective inhibitor of cholesterol biosynthesis via lowering of the low density lipoprotein cholesterol (LDL-C). These effects have made this molecule attractive for the treatment of combined hyperlipidemia, a common atherogenic disorder in clinical practice, and thus also for the prevention of atheroma progression.

Studies have also established that lowering LDL-C levels affords protection from coronary heart disease (see, for example, the "Scandinavian Simvastatin Survival Study" or 4S study, published in The Lancet, 1994, Vol. 344, pp. 1383-1389, or the study on the "Prevention of coronary heart disease with privastatin in men with hypercholesterolemia", published by Shepherd et al. in The New England Journal of Medicine, 1995, Vol. 333, pp. 1301-1307).

Further studies are ongoing to assess the protective capacity of statins against the rate of heart attacks, stroke and coronary heart disease in non-insulin dependent diabetics: the "Collaborative Atorvastatin Diabetes Study" or CARDS study, the "Atorvastatin Versus Revascularisation Treatment" or AVERT study, and the "Anglo-Scandinavian Cardiac Outcomes trial or ASCOT study.

As already mentioned above, since hypertension frequently coexists with hyperlipidemia, and since both are major risk factors for the development of cardiovascular diseases, which often result in adverse cardiovascular events, it would be advantageous for patients to have a single therapy which prevents or treats both of these conditions.

Furthermore, it would be advantageous if the combined therapy would also improve the prevention or treatment of cardiopulmonary, pulmonary or renal diseases, for which it has been found that ANG II antagonists are effective.

Combined treatments and corresponding compositions comprising HMG-CoA reductase inhibitors and ANG II antagonists have already been suggested.

WO 95/26188 discloses a method for the treatment of atherosclerosis and for reducing cholesterol, using an HMG-CoA reductase inhibitor and an ANG II antagonist. Pravastatin, Simvastatin and Lovastatin are cited as possible HMG-CoA reductase inhibitors to be used. Losartran is cited as possible ANG II antagonist to be used.

WO 97/37688 discloses the combined use of HMG-CoA reductase inhibitors and of ANG II antagonists, for the treatment of numerous conditions, among which hypertension and atherosclerosis. Pravastatin, Simvastatin, Lovastatin, and Fluvastatin are cited as possible HMG-CoA reductase inhibitors to be used.

WO 99/11260 discloses the combined use of a specific HMG-CoA reductase inhibitor and of ANG II antagonists, for lowering blood pressure and lipid levels, and for treating angina pectoris and atherosclerosis in a mammal. The specific HMG-CoA reductase inhibitor is atorvastatin. Losartran, irbesartan and valsartan are cited as possible ANG II antagonists to be preferably used. Other cited ANG II antagonists are candesartan and eprosartan.

WO 00/45818 discloses the combined use of an HMG-CoA reductase inhibitor and an ANG II antagonist, for the improvement of diabetic neuropathy, and more specifically for improving nerve conduction velocity and nerve blood flow in patients suffering diabetes. Cited examples of possible combinations are combinations of the statins pravastatin, simvastatin, cerivastatin, fluvastatin, atorvastatin and statin (E), together with the ANG II antagonists losartan, irbesartan, valsartan and candesartan, and preferably candesartan.

WO 01/15674 discloses the combination of an inhibitor of the renin-angiotensin system together with an other antihypertensive, a cholesterol lowering agent, a diuretic or aspirin, for the prevention of cardiovascular events, such as stroke, congestive heart failure, cardiovascular death, myocardial infarction, worsening of angina, cardiac arrest, revascularisation procedures, diabetes and diabetic complications. Cited examples of possible combinations are the combinations of inhibitors of angiotensin-converting enzyme (ACE), i.e. compounds with approved names ending in "-pril", such as captopriol, imidapril, ramipril, etc..., with

the cholesterol lowering agent lovastatin, pravastatin, simvastatin or fluvastatin.

Summary of the Invention

It has been found that co-administration of an effective amount of a specific ANG II antagonist, namely telmisartan, with an effective amount of a specific HMG-CoA reductase inhibitor, namely atorvastatin, or of polymorphs or salts thereof, provides unexpected advantages in the prevention or treatment of cardiovascular, cardiopulmonary, pulmonary or renal diseases, to a person in need of such treatment, with high efficacy, independently of the known blood pressure reducing activity of the ANG II antagonist, and independently of the antihyperlipidemia activity of the HMG-CoA reductase inhibitor, in comparison to administration of the ANG II antagonist or HMG-CoA reductase inhibitor alone.

It has been further found that the prevention or treatment improves endothelial function and provides an organo-, tissue- and vasculo-protection in diseases associated with a need for control of both blood pressure and lipid levels.

It has also been found that the prevention or treatment is especially effective for:

indications (A) which can be positively influenced by an inhibition of the AT_1 receptor mediated effects and a maintenance of the AT_2 receptor mediated effects of Angiotensin II (ANG II), and by an inhibition of the HMG-CoA

reductase effects, thus also increasing bradykinin mediated effects and providing antihyperlipidemic effects; or

indications (B) associated with an increase of AT_1 receptors in the sub-epithelial area or an increase of AT_2 receptors in the epithelia.

Suitable indications (A) are indications selected from:

treatment of combined hypertension and hyperlipidemia;

reduction of the incidence of stroke, acute myocardial infarction or cardiovascular death, especially in persons having elevated risk of adverse cardiovascular events or stroke;

provision of a renoprotection, such as in renal failure or diabetic nephropathy;

prevention of left ventricular hypertrophy, vascular thickening, such as prevention of the thickening of blood vessel walls after vascular operations, improvement of survival after cardiac transplantation, prevention of arterial restenosis after angioplasty, prevention or treatment of atherogenic disorders, such as atherosclerosis, protection against coronary artery disease, prevention of atheroma progression, prevention of diabetic angiopathy;

lowering of cholesterol, lowering of plasma fibrinogen and plasma viscosity, inhibition of smooth muscle cell proliferation, reduction of the ability of macrophages

to oxidize LDL, protection of cardiomyocytes against hypoxic injury, lowering of plasminogen activator inhibitor-1 (PAI-1);

prevention or treatment of ischaemic peripheral circulatory disorders, myocardial ischaemia (angina); and

prevention of the progression of cardiac insufficiency after myocardial infarction.

Suitable indications (B) are indications selected from:

obstructive airways diseases, chronic obstructive pulmonary disease, such as bronchitis or chronic bronchitis, emphysema, likewise from asthma, cystic fibrosis, interstitial lung disease, lung cancer, pulmonary vascular disease, and increased resistance to airflow during forced expiration;

adults respiratory distress syndrome (ARDS), reduction of the proliferative capacity of the epithelium in lung and breast cancer, treatment of sepsis syndrome, lung injury forms, such as pneumonia aspiration of gastric content, chest trauma, shock, burns, fat emboli, cardiopulmonary bypass, O_2 toxicity, haemorrhagic pancreatitis, interstitial and bronchoalveolar inflammation, proliferation of epithelial and interstitial cells, collagen accumulation and fibrosis.

Thus, the present invention provides a method for the prevention or treatment of hypertension and hyperlipidemia in a mammal, comprising co-administration of an effective amount

of the HMG-CoA reductase inhibitor atorvastatin, or of a polymorph or salt thereof, together with an effective amount of the ANG II antagonist telmisartan, or of a polymorph or salt thereof.

The present invention provides also the combined use of telmisartan with atorvastatin, or the combined use of polymorphs or salts of these active compounds, for the manufacture of a pharmaceutical composition for the prevention or treatment of hypertension combined with hyperlipidemia.

Thus, the beneficial efficacy of the methods in accordance with the invention are mainly based on the organo-protective, tissue-protective and vasculo-protective effects of the combined treatment.

The unexpected advantages mentioned above may be due to a more efficient blockade of the AT_1 receptor mediated effects of ANG II, to the AT_2 receptor mediated action of ANG II, left unaffected by this specific ANG II antagonist, together with an increase of the bradykinin mediated effects and the provision of an antihyperlipidemic effect by the specific HMG-CoA reductase inhibitor.

For example, it has been found that the co-administration of the specific ANG II antagonist telmisartan with the specific HMG-CoA reductase inhibitor atorvastatin, or the co-administration of polymorphs or salts of these active compounds, provides a significant prevention of cardio-vascular death and all-cause mortality, especially with regard to incidence of stroke and acute myocardial

infarction, when compared to administration of any of these active compounds alone.

Therefore, a preferred method in accordance with the present invention is to reduce the incidence of stroke and acute myocardial infarction in the human or non-human mammalian body in need thereof, especially in persons having elevated risk of adverse cardiovascular events or stroke, by co-administration of telmisartan with atorvastatin, or by co-administration of polymorphs or salts of these active compounds.

Furthermore, it has been found that combined treatment and corresponding compositions specifically comprising an amount of the HMG-CoA reductase inhibitor atorvastatin together with an amount of the ANG II antagonist telmisartan or, respectively, of polymorphs or salts of these active compounds, are highly active in regulating blood pressure and regulating lipids in a mammal. It is expected that the synergistic effect provided by this specific combination is surprisingly superior over corresponding combinations known in the art.

A synergistic combination according to the invention for regulating blood pressure and regulating lipids is meant to comprise an amount of atorvastatin and an amount of telmisartan, or of polymorphs or salts of these active compounds, wherein the amount of the individual agent alone is insufficient to achieve the therapeutic effect achieved by the administration of the combination of said agents and wherein the combined effects of the amounts of the therapeutic agents is greater than the sum of the therapeutic

effects achievable with the amounts of the individual therapeutic agents.

Viewed from a different aspect, the present invention also relates to pharmaceutical compositions for the treatment of the human or non-human mammalian body for preventing or treating the diseases or indications mentioned hereinbefore comprising a specific ANG II antagonist and a specific HMG-CoA reductase inhibitor, optionally together with pharmaceutically acceptable diluents and/or carriers, as a combined preparation for simultaneous, separate or sequential use in the prevention or treatment of said diseases or indications.

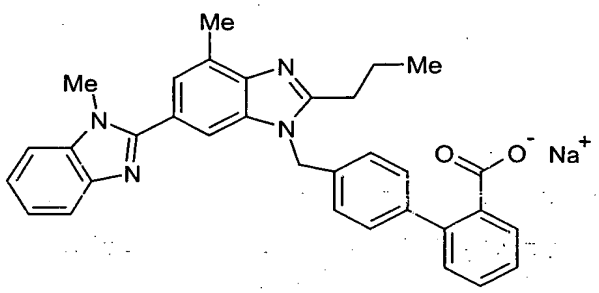
Viewed from a further aspect, the present invention provides the use of a selective ANG II antagonist in combination with a specific HMG-CoA reductase inhibitor, for the manufacture of a pharmaceutical composition for the prevention or treatment of the diseases or indications mentioned hereinbefore.

Detailed Description of the Invention

With regard to all aspects of the invention, the specific ANG II antagonist is telmisartan {4'-[2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)benzimidazol-1-ylmethyl]biphenyl-2-carboxylic acid}, or one of its polymorphs or salts, preferably its sodium salt. Telmisartan is already sold on the market under, for example, the trade name Micardis®.

Telmisartan is disclosed, for example, in EP 0 502 314 and US 5,591,762. Polymorphs of telmisartan are disclosed, for example, in WO 00/43370, US 6,358,986 and US 6,410,742. Sodium salts of telmisartan are disclosed, for example, in unpublished German patent application DE 101 53 737.9.

For example, in accordance with what is disclosed in DE 101 53 737.9, the sodium salt of telmisartan of formula



may be selectively obtained by a suitable choice of manufacturing conditions in a crystalline polymorphic form.

This crystalline form of the sodium salt of telmisartan is characterised by a melting point of T = 245 ± 5°C (determined by DSC = Differential Scanning Calorimetry, using a Mettler-Toledo DSC82 apparatus; heating rate: 10 K/min).

For the manufacture of telmisartan sodium salt, a procedure in accordance with one of the following two manufacture procedures may be used.

Manufacture procedure 1: Preparation of crystalline telmisartan-sodium salt starting from telmisartan.

The starting material used to prepare crystalline telmisartan-sodium salt may be the free acid of telmisartan, which may be obtained by methods known from the prior art (e.g. according to EP 0 502 314).

154.4 g of telmisartan are placed in 308.8 ml of toluene in a suitable reaction vessel. The suspension is combined with 27.8 g of 44.68% sodium hydroxide solution and 84.9 ml of ethanol and heated to 78°C for about 30 min, then the mixture is filtered. If desired, if large amounts of solid are left in the filter, this may be washed with a mixture of 61.8 ml of toluene and 15.3 ml of ethanol.

463.2 ml of toluene are placed in another reaction vessel and refluxed. The filtrate obtained by the process described above is slowly added thereto at boiling temperature and simultaneously distilled off azeotropically. After it has all been added, the solution which may have been obtained from washing the filter is also added and again distilled off azeotropically. The mixture is distilled at up to 103°C and the suspension is allowed to cool to ambient temperature. The crystals are suction filtered, washed with 154.4 ml of toluene and dried at 60°C in the circulating air drier.

Yield: 154.6 g (96%)
Colourless crystals

$C_{33}H_{29}N_4O_2Na \times 0,5H_2O$	calc.:	C 72.51	H 5.72	N 10.25
	found:	C 72.57	H 5.69	N 10.21

Manufacture procedure 2: Preparation of crystalline telmisartan-sodium salt starting from telmisartan hydrochloride.

Preparation of telmisartan-hydrochloride: 411 g of *tert.*-butyl 4´-[[2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-

benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylate are suspended in 822 ml of glacial acetic acid and combined with 213 g of concentrated aqueous hydrochloric acid (37%). The mixture is refluxed and about 640 ml of solvent are distilled off. The residue remaining is slowly combined with about 620 ml of water at 50-60°C. To this mixture are added 20 g of activated charcoal (e.g. Norit SX 2 Ultra) and the resulting mixture is stirred for about 10 min at constant temperature. After filtering, the residue is washed three times with 25 ml of glacial acetic acid and about 620 ml of water. The filtrate obtained is again heated to about 50-60°C and about 2 L of water are added. After stirring for about 12 hours at about 23°C the crystals formed are suction filtered and washed twice with about 500 ml of water, once with about 900 ml of acetone and then dried at about 60°C.

Yield: 367 g (92.5%)
Colourless crystals
Melting point: 278°C

Preparation of crystalline telmisartan sodium salt from telmisartan hydrochloride: 55.1 g of telmisartan hydrochloride are taken up in 110.2 ml of toluene, 5.5 ml of water, 55.1 ml of isopropanol and this mixture is combined with 36.9 g of sodium methoxide (30% in methanol) and 2.75 g of activated charcoal (e.g. Sorit SX 2 Ultra). The mixture is then heated to about 75°C, and about 50 ml of solvent mixture are distilled off at constant temperature over about 30 min. The suspension obtained is filtered and the residue is washed with about 20 ml of toluene. The filtrate is combined with about 5 ml of water and about 150 ml of toluene. The mixture obtained is refluxed. During this time about 150 ml of solvent mixture are azeotropically distilled off (at up to 102°C). The mixture is left to crystallise for one hour at

100°C. The crystals are suction filtered, washed with about 50 ml of toluene and dried at about 60°C.

Yield: 53.6 g (99%)
Colourless crystals

$C_{33}H_{29}N_4O_2Na \cdot 0.5H_2O$	calc.:	C 72.51	H 5.72	N 10.25
	found:	C 72.44	H 5.68	N 10.20

With regard to all aspects of the invention, the specific HMG-CoA reductase inhibitor is atorvastatin, or one of its polymorphs or salts, preferably its hemi calcium salt {[R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt} already sold on the market under, for example, the trade names Lipitor®, Zarator® and Sortis®.

Atorvastatin is disclosed, for example, in EP 0 247 633 and US 4,681,893. Polymorphs of atorvastatin are disclosed, for example, in WO 97/03958, WO 97/03959, EP 0 848 704 and EP 1 148 049. Salts of atorvastatin (monopotassium, monosodium, calcium, magnesium, zinc and meglumine) are disclosed, for example, in EP 0 409 281 and US 5,273,995.

Co-administration of the specific ANG II antagonist and the specific HMG-CoA reductase inhibitor is meant to include administration sequential in time or simultaneous administration, the simultaneous administration being preferred. For sequential administration, the ANG II antagonist can be administered before or after administration of the HMG-CoA reductase inhibitor.

The active compounds can be administered orally, bucally, parenterally, by inhalation spray, rectally or topically, the oral administration being preferred. Parenteral administration may include subcutaneous, intravenous, intramuscular and intrasternal injections and infusion techniques.

The active compounds can be orally administered in a wide variety of different dosage forms, i.e., they may be formulated with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, aqueous suspensions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents. Moreover, such oral pharmaceutical formulations can be suitably sweetened and/or flavoured by means of various agents of the type commonly employed for such purposes. In general, the compounds of this invention are present in such oral dosage forms at concentration levels ranging from about 0.5% to about 90% by weight of the total composition, in amounts which are sufficient to provide the desired unit dosages. Other suitable dosage forms for the compounds of this invention include controlled release formulations and devices well known to those who practice in the art.

For purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch and preferably potato or tapioca starch, alginic acid and certain complex silicate, together with binding agents such as polyvinylpyrrolidone, sucrose,

gelatine and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc or compositions of a similar type may also be employed as fillers in soft and hard-filled gelatine capsules; included lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavouring agents, colouring matter or dyes and, if so desired, emulsifying agents and/or water, ethanol, propylene glycol, glycerine and various like combinations thereof.

For purposes of parenteral administration, solutions of the compounds in sesame or peanut oil or in aqueous propylene glycol may be employed, as well as sterile aqueous solutions of the corresponding pharmaceutically acceptable salts. Such aqueous solutions should be suitably buffered if necessary, and the liquid diluent rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular and subcutaneous injection purposes. In this connection, the sterile aqueous media employed are readily obtained by standard techniques well known to those skilled in the art. For instance, distilled water is ordinarily used as the liquid diluent and the final preparation is passed through a suitable bacterial filter such as a sintered glass filter or a diatomaceous earth or unglazed porcelain filter. Preferred filters of this type include the Berkefeld, the Chamberland and the Asbestos Disk-Metal Seitz filter, wherein the fluid is sucked into a sterile container with the aid of a suction pump. The necessary steps should be taken throughout the

preparation of these inject-able solutions to insure that the final products are obtained in a sterile condition.

For purposes of transdermal administration, the dosage form of the particular compound or compounds may include, by way of example, solutions, lotions, ointments, creams, gels, suppositories, rate-limiting sustained release formulations and devices therefor. Such dosage forms comprise the particular compound or compounds and may include ethanol, water, penetration enhancer and inert carriers such as gel-producing materials, mineral oil, emulsifying agents, benzyl alcohol and the like.

The HMG-CoA reductase inhibitor atorvastatin, or its polymorph or salt, may be administered in a daily dosage of, about 1.25 mg (or 0.018 mg/kg body weight, based on a person of 70 kg) to about 450 mg (6.43 mg/kg body weight, based on a person of 70 kg) orally, about 20 mg (0.286 mg/ kg body weight, based on a person of 70 kg) parenterally, preferably of about 2.5 mg (0.036 mg/kg body weight, based on a person of 70 kg) to about 80 mg (1.428 mg/kg body weight, based on a person of 70 kg) orally. Particularly preferred is an oral daily dosage of about 5 mg (0.071 mg/kg body weight, based on a person of 70 kg), about 10 mg (0.143 mg/kg body weight, based on a person of 70 kg), about 20 mg (0.286 mg/kg body weight, based on a person of 70 kg), or about 40 mg (0.571 mg/kg body weight, based on a person of 70 kg), or specifically a starting oral daily dose of about 10 mg (0.143 mg/kg body weight, based on a person of 70 kg) orally.

The ANG II antagonist telmisartan, or its polymorph or salt, may be administered in a daily dosage of 10 mg (or

0.143 mg/kg body weight, based on a person of 70 kg) to 500 mg (7.143 mg/kg body weight, based on a person of 70 kg) orally and of about 20 mg (0.286 mg/kg body weight, based on a person of 70 kg) parenterally, preferably of 20 mg (0.286 mg/kg body weight, based on a person of 70 kg) to 100 mg (1.429 mg/kg body weight, based on a person of 70 kg) orally. Particularly preferred is an oral daily dosage of 40 mg (0.571 mg/kg body weight, based on a person of 70 kg) to 80 mg (1.143 mg/kg body weight, based on a person of 70 kg) or specifically of about 80 mg (1.143 mg/kg body weight, based on a person of 70 kg).

Preferably, the ratio of atorvastatin to telmisartan, or of their polymorphs or salts, in the pharmaceutical combination is from 1:100 to 100:1 by weight.

In the most preferred embodiments, atorvastatin, or a polymorph or salt thereof, is administered simultaneously together with telmisartan, or a polymorph or salt thereof, via the oral route, in a daily dosage of:

10 mg atorvastatin and 40 mg telmisartan
(or polymorphs or salts thereof);
10 mg atorvastatin and 80 mg telmisartan
(or polymorphs or salts thereof);
20 mg atorvastatin and 40 mg telmisartan
(or polymorphs or salts thereof);
20 mg atorvastatin and 80 mg telmisartan
(or polymorphs or salts thereof).

In a preferred embodiment, the pharmaceutical compositions of this invention contain the HMG-CoA reductase

inhibitor in an amount of 1.25 mg to 450 mg, and the ANG II antagonist in an amount of 10 mg to 500 mg, in single dosage units, optionally together with one or more pharmaceutically acceptable diluents and/or carriers.

In a further preferred embodiment, the pharmaceutical compositions of this invention contain the HMG-CoA reductase inhibitor in an amount of 2.5 mg to 80 mg, and the ANG II antagonist in an amount of 20 to 100 mg, in single dosage units, optionally together with one or more pharmaceutically acceptable diluents and/or carriers.

A further preferred subgroup of pharmaceutical compositions of this invention contain the HMG-CoA reductase inhibitor in an amount of 5 mg to 20 mg, and the ANG II antagonist in an amount of 40 mg to 80 mg, in single dosage units, optionally together with one or more pharmaceutically acceptable diluents and/or carriers.

A further preferred subgroup of pharmaceutical compositions of this invention contain the HMG-CoA reductase inhibitor in an amount of 10 or 20 mg, and the ANG II antagonist in an amount of 40 or 80 mg, in single dosage units, optionally together with one or more pharmaceutically acceptable diluents and/or carriers.

As already mentioned above the present invention also provides the use of a specific ANG II antagonist for the manufacture of a pharmaceutical composition for the treatment of the human or non-human mammalian body for preventing or treating the indications mentioned hereinbefore when used in combination with a specific HMG-CoA reductase inhibitor. This

use aspect is meant to include the manufacture of all pharmaceutical compositions mentioned hereinbefore in accordance with the invention.

CLAIMS

1. A method for the prevention or treatment of cardiovascular, cardiopulmonary, pulmonary or renal diseases, which method comprises co-administration of effective amounts of the active compounds telmisartan and atorvastatin, or of polymorphs or salts thereof, to a person in need of such treatment.

2. The method in accordance with claim 1, wherein the active compounds are the sodium salt of telmisartan and the calcium salt of atorvastatin.

3. The method in accordance with claim 1 or 2, wherein the prevention or treatment improves endothelial function and provides an organo-, tissue- and vasculo-protection in diseases associated with a need for blood pressure level and lipid level control.

4. The method in accordance with any one of claims 1 to 3, wherein the prevention or treatment is for:

indications (A) which can be positively influenced by an inhibition of the AT_1 receptor mediated effects and a maintenance of the AT_2 receptor mediated effects of Angiotensin II (ANG II), and by an inhibition of the HMG-CoA reductase effects, thus also increasing bradykinin mediated effects and providing antihyperlipidemic effects; or

indications (B) associated with an increase of AT_1 receptors in the sub-epithelial area or an increase of AT_2 receptors in the epithelia.

5. The method in accordance with claim 4, characterised in that the indications (A) are selected from:

treatment of combined hypertension and hyperlipidemia,

reduction of the incidence of stroke, acute myocardial infarction or cardiovascular death, especially in persons having elevated risk of adverse cardiovascular events or stroke;

provision of a renoprotection, such as in renal failure or diabetic nephropathy;

prevention of left ventricular hypertrophy, vascular thickening, such as prevention of the thickening of blood vessel walls after vascular operations, improvement of survival after cardiac transplantation, prevention of arterial restenosis after angioplasty, prevention or treatment of atherogenic disorders, such as atherosclerosis, protection against coronary artery disease, prevention of atheroma progression, prevention of diabetic angiopathy;

lowering of cholesterol, lowering of plasma fibrinogen and plasma viscosity, inhibition of smooth muscle cell proliferation, reduction of the ability of macrophages to oxidize LDL, protection of cardiomyocytes against

hypoxic injury, lowering of plasminogen activator inhibitor-1 (PAI-1);

prevention or treatment of ischaemic peripheral circulatory disorders, myocardial ischaemia (angina); and

prevention of the progression of cardiac insufficiency after myocardial infarction.

6. The method in accordance with claim 4, characterised in that the indications (B) are selected from:

obstructive airways diseases, chronic obstructive pulmonary disease, such as bronchitis or chronic bronchitis, emphysema, likewise from asthma, cystic fibrosis, interstitial lung disease, lung cancer, pulmonary vascular disease, and increased resistance to airflow during forced expiration;

adults respiratory distress syndrome (ARDS), reduction of the proliferative capacity of the epithelium in lung and breast cancer, treatment of sepsis syndrome, lung injury forms, such as pneumonia aspiration of gastric content, chest trauma, shock, burns, fat emboli, cardiopulmonary bypass, O_2 toxicity, haemorrhagic pancreatitis, interstitial and bronchoalveolar inflammation, proliferation of epithelial and interstitial cells, collagen accumulation and fibrosis.

7. A method for the prevention or treatment of hypertension and hyperlipidemia in a mammal comprising co-administration of an effective amount of the active compound

atorvastatin together with an effective amount of the active compound telmisartan, or of polymorphs or salts thereof.

8. The method in accordance with claim 7, wherein the active compounds are the sodium salt of telmisartan and the calcium salt of atorvastatin.

9. The method in accordance with any of claims 1 to 8, characterised in that atorvastatin, or its polymorph or salt, is administered in a daily dosage of about 0.018 mg/kg body weight to 6.43 mg/kg body weight orally, and telmisartan, or its polymorph or salt, is administered in a daily dosage of about 0.143 mg/kg to 7.143 mg/kg body weight orally.

10. The method in accordance with any of claims 1 to 8, characterised in that atorvastatin, or its polymorph or salt, is administered in a daily dosage of about 0.286 mg/kg body weight parenterally, and telmisartan, or its polymorph or salt, is administered in a daily dosage of about 0.286 mg/kg body weight parenterally.

11. Pharmaceutical composition for the treatment of the human or non-human mammalian body, for the prevention or treatment of the diseases or indications mentioned in claims 1 and 3 to 7, comprising atorvastatin and telmisartan, or polymorphs or salts thereof, as a combined preparation for simultaneous, separate or sequential use in treatment of said diseases or indications, optionally together with one or more pharmaceutically acceptable diluents and/or carriers.

12. The pharmaceutical composition in accordance with claim 11 wherein the ratio of atorvastatin to telmisartan, or

of polymorphs or salts thereof, is from 1:100 to 100:1 by weight.

13. The pharmaceutical composition in accordance with claim 11 or 12, wherein the ratio of atorvastatin to telmisartan, or of polymorphs or salts thereof, is from 1:10 to 10:1 by weight.

14. The pharmaceutical composition in accordance with any one of claim 11 to 13, wherein the ratio of atorvastatin to telmisartan, or of polymorphs or salts thereof, is from 1:2 to 1:8 by weight.

15. The pharmaceutical composition in accordance with any one of claims 11 to 13, comprising atorvastatin or a polymorph or salt thereof in an amount of 10 mg to 100 mg, and telmisartan or a polymorph or salt thereof in an amount of 10 to 100 mg, in single dosage units.

16. Use of telmisartan, or a polymorph or salt thereof, in combination with atorvastatin, or a polymorph or salt thereof, for the manufacture of a pharmaceutical composition in accordance with any one of claims 11 to 15, for the prevention or treatment of the diseases or indications mentioned in claims 1 and 3 to 7, in a human or non-human mammalian body.

17. Use of telmisartan, or a polymorph or salt thereof, in combination with atorvastatin, or a polymorph or salt thereof, for the manufacture of a pharmaceutical composition in accordance with any one of claims 11 to 15, for the

prevention or treatment of hypertension combined with hyperlipidemia.

ABSTRACT

The present invention relates to a pharmaceutical combination for the prevention or treatment of cardiovascular, cardiopulmonary, pulmonary or renal diseases, by improving endothelial function and providing an organo-, tissue- and vasculo-protection in indications associated with a need for blood pressure level and lipid level control. The invention also relates to a method for the prevention or treatment of these diseases, comprising co-administration of effective amounts of specific active compounds in a ratio which provides an additive and synergistic effect, and to the combined use of these specific compounds for the manufacture of corresponding pharmaceutical combination compositions.